REMARKS

In response to the Final Office Action mailed on January 20, 2010, the Applicants herewith submit a Request for Continued Examination (RCE) in compliance of 27 C.F.R. 1.114 and a Petition for Three Month Extension of Time.

Summary of claim amendments:

Applicants have cancelled claim 24 and amended claim 28 to direct the subject already has a preformed or terminally full thrombosis. The amendment to claim 28 is supported throughout the specification, for example, at paragraphs [0014] and [0016] of the published application. Applicants have also amended claims 25 and 26 to now be dependent on claim 28. Support for new claims 29 and 30 can be found throughout the specification, for example, in original claim 9, as well as paragraphs particular in [0066] and [0116]-[0122] of the published application. Additional support for new claim 30 is found throughout the application, in particular, paragraphs [0066], [0072], [0083] and [0117], as well as paragraphs [0054]-[0056], [0064] [0069] and [0071] of the published application, as well as in the Working Examples, in particular Example 3 and paragraphs [0112] and [0122] and Figure 2. Support for claim 31 is found throughout the application, particularly at paragraphs [0064], [0086] and [0107] of the published application.

Accordingly, Applicants submit that no new matter has been added by virtue of these amendments or the new claim, and their entry is respectfully requested.

Claim Rejections under 35 U.S.C. §103(a) (Obviousness)

The Examiner has raised a number of rejections to the claims under 35 U.S.C. §103(a), including rejection of claims 24 and 26 as allegedly being obvious in view of DePetrrillo *et al.,* (US Patent Application 2002/0115665), rejection of claims 24 and 25 for allegedly being obvious in view of Hisamichi *at al.,*. (U.S. Patent 6,432,963), and rejection of claim 28 for allegedly being obvious in view of DePetrrillo *et al.,* in view of Hisamichi *at al.,* in light of the legal decision in In re: Kerkhoven.

Applicants respectfully disagree. However, in order to expedite the prosecution, Applicants have cancelled Claim 24 rending the obviousness rejection under 35 U.S.C. § 103(a) moot with respect to Claim 24.

Claim 28 is now directed to a method for promoting fibrinolysis in a subject in need having a preformed or terminally full thrombus. There is simply nothing in tge conmination that suggest a *syk* inhibitor has anything to do with fibrinolysis. Nor is there anything to suggest that a calpain inhibitor can be used to dissolve an already formed thrombus by the process of fibrinolysis. This is more fully discussed below.

Support for the amendment to Claim 28 can be found throughout the specification, in particular, at paragraphs [0014] and [0016], and Example 3. Applicants respectfully submit the amendments to the claims have obviated the 103(a) rejections as discussed in more detail below and respectfully request their withdrawal.

(A) As Applicants have cancelled claim 24, the rejection under 35 U.S.C. § 103(a) of claims 24 and 26 in view of DePetrillo is now moot, and respectfully request withdrawal of the rejection.

(B) As Applicants have cancelled claim 24, the rejection under 35 U.S.C. § 103(a) of claim 24 in view of Hisamichi is now moot, and respectfully request withdrawal of the rejection.

(C) The Examiner has rejected claim 28 as allegedly being obvious DePetrrillo, in view of Hisamichi *at al.,* in light of the legal decision in In re: Kerkhoven.

Applicants as aforesaid respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

DePetrillo *et al.*, discusses use of a calpain inhibitor to inhibit *platelet aggregation*, which is the *formation* of the thrombus, does not necessary mean that the calpain inhibitor can dissolve an *already* formed thrombus, by the process of *fibrinolysis*.

In particular, as discussed in our Response dated November 6, 2009, it is well known that platelet agglutination and prevention of thrombus formation involve completely different biological phenomena and pathways than fibrinolysis and dissolving of an existing thrombus.

The process of formation of thrombosis is therefore a *distinct* process from the process of fibrinolysis. Applicants state in paragraph [0005] and [0006] in the published application.

> "[0005] ***Platelet aggregation*** refers to the *adherence of platelets to each other*, typically at the site of blood vessel damage. Clot retraction describes the contractile ability of platelets to consolidate or shrink the size of the blood clot once it has formed....***Fibrinolysis,*** also known as clot lysis, refers to the process through which *thrombi dissolve*, as a consequence of activation of the fibrinolytic system."
>
> "[0006] Platelet aggregation, clot retraction, and fibrinolysis are important ***parts*** of thrombus regulation".

In paragraph [0029] Applicants state:

> "A pathological process called ***thrombosis*** results when *platelet aggregation* and/or a fibrin clot blocks (i.e., occludes) a blood vessel."

Accordingly, platelet aggregation and fibrinolysis are separate and *distinct processes* in the regulation of thrombosis. As discussed previously in Applicants Response dated November 6, 2009, fibrinolysis is a process by which an *existing* and *fully-formed* clot is broken down by enzymes, such as plasmin into fibrin degradation products. In fact, the process of *fibrinolysis* is *actively inhibited by the presence of platelets*, which secrete molecules such as plasminogen activator inhibitors which inhibit the formation of active plasmin enzyme from its precursor plasminogen. Accordingly, presence of *platelets inhibits fibrinolysis*.

Platelet aggregation and fibrinogeneis involve completely different factors and pathways. Thus, agents which *prevent thrombotic platelet aggregation* function by a completely different way as compared to agents which *inhibit fibrinolysis* (dissolving a clot) of existing thrombi. Thus, Applicants submit that an anti-thrombotic effect of calpain inhibitors referenced in DePetrillo does not indicate the calpain inhibitors exhibit the ability to promote fibrinolysis.

Moreover, Applicants teach that an agent which inhibits the process platelet aggregation and thrombosis formation, for example, a calpain inhibitor, does not necessary function to break down the clot in the process of fibrinolysis. Applicants state in paragraph [0014] (and also, similarly in paragraph [0116]) in the published application:

> "Anti-thrombotic agents can block or *inhibit thrombus formation*, as discussed above; however, they are ***not very effective in dissolving a pre-formed thrombus or to help in fibrinolysis***. Thus, terminal thrombus formation may cause myocardial infarction and/or ischemic chest pain. Instead, the *current treatment*

for total blockage by thrombus formation is either angio-balloon-plasty and/or bypass surgery.

Accordingly, one of ordinary skill in the art would expect that an agent e.g., a *calpain inhibitor* which inhibits thrombosis formation would be **ineffective** at dissolving a pre-formed thrombosis (e.g., fibrinolysis). Furthermore, nowhere does DePetrillo teach or even suggest use of a calpain inhibitor in a method for **dissolving an existing clot**, *i.e.*, for fibrinolysis. A skilled artisan reading the DePetrillo reference and without additional data would not conclude that inhibition of calpain activity can be used to promote fibrinolysis of an *existing pre-formed thrombus*. Only in hindsight after reading the instant specification, which provides working examples using exemplary calpain inhibitors would a skilled artisan know that a calpain inhibitor, ***in combination*** with a *syk* kinase inhibitor promotes fibrinolysis of a pre-formed clot. Moreover, based on the teachings of DePetrillo, one of ordinary skill in the art could not have even expected the calpain inhibitor therapy to work because there is no reference of these agents being capable of dissolving an *existing* thrombi. Furthermore, no *in vitro* assay existed to assess whether an agent had such an activity.

Accordingly, prior to the instant invention, a skilled artisan reading DePetrillo *et al.,* would not have had reason to believe that an inhibitor of platelet aggregation, e.g., a calpain inhibitor would promote fibrinolysis in a *pre-formed clot*. Further, a skilled artisan certainly would have no reason to come up with an embodiment of the present invention, namely *combining* an inhibitor of thrombosis, such as an inhibitor of calpain ***with*** an inhibitor of *syk* kinase to come up with the present invention to promote fibrinolysis (claim 32). Even if a skilled artisan were to contemplate such a combination, as discussed in our previous response, there was no such *in vitro* assay available to determine the effect of such a combination of agents on fibrinolytic activity in the presence of platelets.

Like DePetrillo, also Hisamichi does not teach a specific advantage or property of a *Syk* inhibitor in a method for dissolving a *pre-existing* clot. Hisamichi only recites a list of diseases that includes those "in which ***platelet agglutination*** takes part." In particular, the Hisamichi reference does not teach or suggest a method to **promote fibrinolysis** or the dissolving a pre-existing clot using *Syk* kinase inhibitors. As explained above, platelet agglutination and fibrinolysis are distinct biological processes, involving completely different pathways. Further, no *in vitro* assay existed to determine whether an agent had fibrinolytic activity in the presence of platelets.

Applicants respectfully submit that Hisamichi does not explicitly discuss use for Syk tyrosine kinase inhibition for promoting fibrinolysis, but rather vaguely references diseases "in which *platelet agglutination takes part*". As such, no where does Hisamichi suggest to one of skill in the art that such inhibition would be effective in the actual dissolution of a thrombus, *i.e.,* fibrinolysis. In contrast, the instant specification discloses working examples demonstrating inhibition of Syk kinase leads to actual fibrinolysis of a pre-formed clot, even in the *presence of platelets*.

Only in hindsight after reading the instant specification, which discusses the use of an *in vitro* assay in the presence of platelets to demonstrate a ***combination*** of exemplary calpain inhibitors ***and*** *syk* kinase inhibitors, would a skilled artisan know that a calpain inhibitor and/or a *syk* kinase inhibitor promotes fibrinolysis of a ***pre-formed clot.*** Moreover, neither DePetrillo or Hisamichi teach one of ordinary skill in the art that a calpain inhibitor in combination with a syk kinase inhibitor would work because there is no reference of either of these agents being capable of dissolving an ***existing pre-formed*** thrombi.

In view of the above, Applicants respectfully submit that the rejection of Claim 28, as amended under 35 U.S.C. § 103(a) in view of DePetrillo *et al* in light of Hisamichi should be withdrawn.

Applicants respectfully submit new claims 29 to 32, where new claim 29 is directed to *in vitro* assay to identify a compound to promote fibrinolysis *in the presence of platelets*, which inhibits calpain activity and sustains eNOS activity. New claim 30 is directed to an *in vitro* method to identify a compound which promotes fibrinolysis in the presence of platelets comprising a two step process of screening a library for compounds which inhibit calpain activity, and then assessing the agent which inhibits calpain activity to identify an agent which sustains eNOS activity in the presence of platelets. Support for the *in vitro* clot lysis assay in the presence of platelets is disclosed in the instant application from paragraphs [0116]-[0122].

Support for new claim 29 is found throughout the application, in particular in [0066] and [0116]-[0122] of the published application. Support for New claim 30 is found throughout the application, in particular, paragraphs [0066], [0072], [0083] and [0117], as well as paragraphs [0054]-[0056], [0064] [0069] and [0071] of the published application. The applicants also demonstrate these claims in the Working Examples, in particular Example 3 and paragraphs

[0112] and [0122] and Figure 2. Support for claim 31 is found throughout the application, particularly at paragraphs [0064], [0086] and [0107] of the published application.

In view of the foregoing, Applicants submit that all issues raised in the Office Action have been addressed herein. Early and favorable action is earnestly solicited.

The Commissioner is hereby authorized to charge fee deficiencies or credit overpayments associated with the instant filing in above-referenced matter to NIXON PEABODY LLP Deposit Account No. 50-0850.

Date: July 20, 2010

Respectfully submitted,

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